REMARKS

The Office Action

The Office Action sets forth the following grounds for rejection:

1. Claims 3, 7, and 18 are rejected under 35 U.S.C. § 112, second paragraph, for an alleged indefiniteness;

2. Claims 1-8 and 11-21 are rejected under 35 U.S.C. § 103(a), as allegedly unpatentable over Masterson et al. (USP 5,580,580); and

3. Claims 8-10 are rejected under 35 U.S.C. § 103(a), as allegedly unpatentable over Masterson et al. in combination with Malmquist-Granlund et al. (USP 5,178,868).

Discussion of Indefiniteness Rejection

Applicants respectfully traverse the indefiniteness rejection.

Regarding Claims 3 and 18, the Office Action requests clarification as to how the polymer can be insoluble in gastric and intestinal juices, as recited in Claim 1, yet erode in the same gastric and/or intestinal juices, as recited in Claims 3 and 18. The Office Action appears to assume that erosion of the polymer requires it to be soluble which is however not correct. Dissolution and erosion are different processes, and dissolution is not a pre-requisite to the process of erosion. As those of skill in the art would appreciate, dissolution produces a solution of the polymer but leaving the polymer molecule intact; dissolution is usually a rapid process occurring within second or minutes. Erosion however may predominantly or exclusively occur through degradation of the polymer due to the action of gastric and/or intestinal juices, and it is usually a slow process. It is immediately apparent from these explanations that a polymer can be erodible in gastric and/or intestinal juices though being insoluble in those juices. Accordingly, there is no ambiguity in the claims, and therefore, the objection of lack of clarity should be withdrawn.

Regarding Claim 7, the Office Action objects to the recited sphericity and suggests clarification and/or evidence of the Wadell standard for sphericity. The sphericity according to Wadell is defined in the paragraph bridging pages 20 and 21 of the present specification. As illustrated, for example, by the enclosed NASA papers, NASA Technical Memorandum 105916 (Zakhem et al., 1993) and NASA/TM-2003-212125 (Stanford et al., 2003), it is a

measure well known to the skilled person since long for describing the shape of particles. Accordingly, there is no ambiguity.

In view foregoing, the indefiniteness rejection should be withdrawn.

Discussion of Obviousness Rejections

1. Claims 1-8 and 11-21. Applicants respectfully traverse this rejection.

The object of the present invention is to provide improved delayed-release formulations which permit a targeted release of active ingredients at a desired site in the gastrointestinal tract, especially in the intestinal tract or colon and which should, therefore, permit release in an essentially pH-independent manner and avoid great variations in residence time in the stomach and in transit time through the intestinal tract and the colon (cf. page 1, lines 3-8 and 33-36; page 6, line 29 to page 7, line 5; page 9, line 4 to page 10, line 6 of the present specification).

In contrast thereto, Masterson et al. relates to administration of mono- or diamino-pyridines in the treatment of neurological diseases, and it has the object to provide a formulation which permits sustained release over not less than a 12 hour period and at a rate sufficient to achieve therapeutically effective blood levels over a period of 12-24 hours in order to enable administration on a once- or twice-daily basis (cf. abstract and col. 2, lines 35-44). Moreover, to obtain a relatively immediate therapeutic response, the formulation of Masterson et al. preferably contains an amount of a rapid release form of the active agent (cf. col. 3, lines 54-57; col. 4, lines 16-19; col. 6, lines 43-56; col., lines 47-55; col. 14, line 65; col. 15, line 47; etc.), which also illustrates that the cited reference does not have the object to provide delayed release at a desired site in the intestinal tract. Masterson et al. is therefore not a pertinent reference to achieve the object of the present invention, namely delayed release at a desired site in the intestinal tract, and would not have been considered by the skilled person in this respect. Even if considered, Masterson et al. would not have rendered obvious the claimed invention for the reasons given below.

To achieve delayed release of active ingredient in the gastrointestinal tract, the present invention proposes a pharmaceutical composition comprising a plurality of coated active ingredient-containing particles, in which release is delayed through a combination of at least three release delaying measures, namely,

(1) matrix retardation by use of a core material which is a homogeneous mixture comprising an active pharmaceutical ingredient and a polymer insoluble in gastric and intestinal juices,

(2) compaction of the core material such that the average pore diameter is decreased to 35 μm or less, measured by mercury porosimetry at 1000 to 4000 bar,

(3) coating the compacted cores with a coating comprising a polymer insoluble in gastric and intestinal juices.

Masterson et al. do not teach or suggest measures (1) and (2), let alone the combination of all three measures.

Masterson et al. teaches the use of conventional granulation and coating techniques to obtain the disclosed formulation comprising a pellet for oral administration. The cited reference does not teach or suggest above measure (2), i.e., compaction of the core material to reduce its average pore diameter to 35 μm or less. Conventional matrix granules have average internal pore diameters of up to about 100 μm, as set forth on page 8, lines 22-24, of the present specification. To achieve an average pore diameter not exceeding 35 μm, as required in accordance with the present invention, application of high pressures, for example 5-30 kN per cm length of press in a roller compactor or roll press, is necessary. Moreover, such compaction usually increases the solid density of the core material by at least about 10% (page 8, line 38 to page 9, line 2; page 20, lines 4-23). Masterson et al. does not contain anything that could have suggested or rendered obvious such compaction of the core material. Furthermore, comminution of compacted core material usually results in irregularly shaped, non-spherical particles (cf. page 20, line 25 to page 21, line 16 of the present specification). The fact that the oral formulation disclosed by Masterson et al. is based on pellets, and that the coated and uncoated cores are usually referred to as "pellets" and "spherical cores" thus also illustrates that compaction was not considered in Masterson et al., nor would compaction be suitable to obtain the pellet formulation disclosed by Masterson et al. Hence, Masterson et al. clearly does not suggest or render obvious the present compacted core material having an average pore diameter not exceeding 35 μm, and it could thus not render obvious the claimed invention for this reason alone.

The Office Action's reference to col. 9, lines 55-62 on page 3 of the Office Action is erroneous. The cited passage does not refer to "completed core." It states: "The pellets or

granulates may be compressed into tablets ... in such a way that the specific dissolution rate of the pellets is maintained." The statement thus clearly excludes application of high pressures that would affect the release characteristics; hence, this statement rather support the above position that Masterson et al. does not teach the present compaction of the core material to further delay release of the active ingredient. Besides, even application of very high pressures in tableting would not lead to compaction of the cores but rather compact the complete tablet formulation, thereby affecting the disintegration characteristics of the tablet, and possibly destroying the sustained-release coatings.

Further, Masterson et al. does not teach or suggest measure (1), i.e. the present core material being a homogeneous mixture comprising an active pharmaceutical ingredient and a polymer insoluble in gastric and intestinal juices.

Col. 2, line 51 to col. 3, line 22 of Masterson et al. gives a general teaching of formulation comprising a pellet for oral administration, wherein said pellet comprises a core of a mono- or di-aminopyridine (or salt thereof) in association with one ore more excipient(s), and a multilayer membrane surrounding said core and containing a major proportion of a film-forming, water insoluble polymer and optionally a minor proportion of a pharmaceutically acceptable film-forming, water soluble polymer. This general teaching does not even mention the presence of a polymer in the core of the pellet. (Besides, the term "excipient(s)" does not include the pertinent polymers, as is apparent from col. 8, lines 35-45.)

Col. 4, lines 26-39 of Masterson et al. teaches that the core of the pellet formulations preferably comprises: a) a powder mixture containing a mono- or di-aminopyridine (or salt thereof) and an excipient, and b) a polymeric material containing a major proportion of a water soluble polymer and a minor proportion of a water insoluble polymer, said core comprising layers of said powder mixture and said polymeric material superimposed one upon the other. The preferred core thus appears to have an onion-like structure with alternate layers of powder mixture and polymeric material and could likewise not teach or suggest the homogeneous mixture used as core material in accordance with the present invention. Moreover, the layers of polymeric material, though being defined as part of the core in Masterson et al., act as sustained-release coating rather than the present matrix retardation, and they contain predominantly water soluble polymers.

Col. 4, line 40 to col. 5, line 43 of Masterson et al. merely teaches examples of water soluble polymers, water insoluble polymers, polymers which are slightly permeable to mono- or di-aminopyridine and water, and polymers with pH-dependent permeability and solubility. This teaching could not suggest the present homogeneous mixture forming the core material, even if read in conjunction with the above teaching, since col. 2, line 51 to col. 3, line 22 do not mention the presence of a polymer in the core, let alone any polymer insoluble in gastric and intestinal juices, and since col. 4, lines 26-39 teaches a layered structure rather than the present homogeneous mixture. Moreover, it is pointed out in this connection that the term "water insoluble polymer", as used in Masterson et al., must not be equated with the present "polymer insoluble in gastric and intestinal juices". The teaching of "water insoluble polymers" in Masterson et al. includes, inter alia, polymers that have pH-dependent solubility such as, for example, Eudragit S which is insoluble in water but becomes soluble in a neutral to weakly alkaline medium and which is thus not deemed to be insoluble in intestinal juices (cf. col. 5, lines 29-43).

Col. 5, line 44 to col. 6, line 42 of Masterson et al. relates to alternative methods for obtaining a core having a number of layers of the core-forming materials. According to this teaching, the active agent, excipient(s) and the polymeric material can be built up on an inert core, preferably a non-pareil seed (col. 5, line 46 to col. 6, line 15), or a central active core (col. 6, lines 16-42). In the latter alternative, a homogeneous powder of mono- or di-aminopyridine, excipient(s) and polymeric material is formed, a portion of this blend is shaped to form a central core, and the remainder of the blend is applied alternately or simultaneously with a polymer binding solution to form a layered structure. However, neither of these alternatives teaches to use a polymer insoluble in gastric and intestinal juices. Moreover, the obtained core appears to be a multi-layer arrangement rather than the present homogeneous mixture. Thus, this passage could not teach or suggest to those of ordinary skill in the art the present invention, especially present measure (1).

Col. 8, lines 14-22 of Masterson et al. is not cited in the Office Action but is marked on the margin. The first sentence states: "Depending on the function of the pellets, the polymeric material of the core or membrane will consist solely of a water insoluble polymer or a polymer which is slightly permeable to water and aqueous solutions of a mono- or di-aminopyridine." However, this statement could not suggest or render obvious the claimed

invention for the following reasons: 1) It does not teach to use a polymer insoluble in gastric and intestinal juices but refers generally to water insoluble and slightly water permeable polymers. 2) It relates the polymeric material contained in the core or membrane and could thus not teach to use a polymer insoluble in gastric and intestinal juices in both the core and the membrane, as required in accordance with the present invention. 3) It does not teach the core to be a homogeneous mixture of active ingredient and polymer but the reference as a whole rather teaches away from this feature, as the more detailed disclosure relating to embodiments utilizing a polymer in the core teach to use the polymer in the form of a layered structure, as explained above. 4) It does not teach compaction of the core material but actually relates to pellets.

Masterson et al. thus provides only a vague generic teaching for an optional use of polymers in the "core", in which case the core however appears to have a layered structure (i.e. the polymer rather acts as release-delaying coating), while the specific teaching in the examples does not include any formulations containing a release-delaying polymer in the core. In Examples 1 and 7, the cores are starch/sugar seeds to which a homogeneous powder of 4-aminopyridine, talc and lactose is applied. In Examples 2 and 8, the cores consist of a homogeneous powder of either 4-aminopyridine or 3,4-diaminopyridine, talc and lactose layered into spherical cores. Examples 3, 4, 6, 9 and 10 utilize the active pellets of Example 2 as cores. In Example 5, the active beads/pellets of Example 1 are used as cores. (Examples 11-27 relate to gels, creams, patches etc. for percutaneous administration and are thus not pertinent.). Present measure (3), i.e. the coating comprising a polymer insoluble in gastric and intestinal juices, is encompassed by the broader generic teaching of Masterson et al. of a multi-layer membrane surrounding the core and containing major proportion of a film-forming, water insoluble polymer and optionally a minor proportion of a film-forming water soluble polymer (col. 2, line 65 to col. 3, line 3). Part of the disclosed water insoluble polymers (col. 4, line 59 to col. 5, line 11), especially Eudragit RS, would seem to be suitable also in accordance with the present invention. Nevertheless, it may be mentioned that the teaching of Masterson et al. does not require the coating polymer to be insoluble in gastric and intestinal juices nor suggest any advantages of such property but the coating polymer may be any other "water insoluble" polymer, for example, an enteric material such as Eudragit S (cf. Examples 1-3 and 9).

Hence, even if a person of ordinary skill would have considered the teaching of Masterson et al., this could not have taught him at least of two of the three release delaying measures of the claimed invention, and that it could thus not have suggested or rendered obvious in any event to the skilled person the combination of those three release delaying measures.

Due to the combination of the at least three release-delaying measures, the claimed composition provides several advantages not suggested by Masterson et al. (cf. pages 9-10 of the present specification). As explained above, it permits targeted release of active ingredients at a desired site in the intestinal tract. Moreover, drug release takes place in an essentially pH-independent manner whereby effects of biological differences between individual patients are avoided, and release characteristics are substantially independent of the shape and size of the particles, thus rendering the production of spherical particles unnecessary. The coated particles possess very high mechanical stability and avoid the risk to impair the release characteristics when compressed into tablets, and the claimed composition can be produced in a highly reproducible manner and at fairly low costs. Furthermore, the claimed invention enables the production of compositions having, if desired, a very high active ingredient content of, for example, up to about 97%, whereby the size of the formulation (e.g. tablet or capsule size) can be significantly reduced but, nevertheless, a sufficient delay of release is achieved. Masterson et al. could not even remotely suggest those advantages nor the combination of delaying measures which made possible those advantages.

In view of the foregoing, the obviousness rejection of claims 1-8 and 11-21 should be withdrawn.

2. Claims 8-10. Applicants respectfully traverse this rejection.

Malmqvist-Granlund et al. is cited to illustrate further active ingredients in addition to the aminopyridines disclosed in Masterson et al. The mere fact that an active ingredient is mentioned in connection with a controlled release formulation in Malmqvist-Granlund et al. does not necessarily imply that administration of said drug on a once- or twice-daily basis in accordance with Masterson et al. would be desirable. However, even if the aminopyridine in the compositions of the Masterson et al. reference were replaced with active ingredients as disclosed by Malmqvist-Granlund et al., this would not have led to or rendered obvious the

claimed compositions for the above reasons which show the unobviousness of the claimed invention irrespective of the active ingredient utilized. Hence, the Malmqvist-Granlund et al. reference could not add anything to the teaching of Masterson et al., as discussed above, that could have rendered obvious the claimed invention.

Malmqvist-Granlund et al. has the object of providing an essentially zero order diffusion controlled release and they teach an oral pharmaceutical controlled release multiple units dosage form in which individual units (cores) containing an active substance are surrounded by a coating essentially consisting of (a) a polymer that is insoluble and non-swellable in and impermeable to water and gastrointestinal fluids, and (b) a water-soluble pore-creating substance. Thus, this reference does not have the object to achieve delayed release at a desired site in the intestinal tract and would not have been considered by the skilled person for this purpose. If nevertheless considered, the disclosed use of a pore-creating substance would rather teach away from the present invention, as explained in response to the first Office Action.

In view of the foregoing, the obviousness rejection of claims 8-10 should be withdrawn.

Conclusion

The application is considered in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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